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EXAMINER
FURMAN, K

ART UNIT	PAPER NUMBER
1814	9

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DATE MAILED: 07/25/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 10-6-94, 4-27-95 and 5-26-95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-5, 10-12 and 26-30 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☑ Claims 6-9 and 13-25 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-5, 10-12 and 26-30 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☑ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☑ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

1. Claims submitted in preliminary amendment of Paper No. 7 and numbered 36-40 having been renumbered as 26-30 since there were no other claims after claim 25 in the application.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR §1.821(a) and (a)(2). However, this application fails to comply with one or more of the requirements of 37 CFR §§ 1.821 through 1.825 as follows: The description and/or claims of the patent application mentions sequences that are not listed in the "Sequence Listing" and/or are not refered to by proper reference sequence identifiers as required by § 1.821(d). See the sequences on 23, 24, 26-31 and 33-35 which are not already in the "Sequence Listing", which sequences are NOT required to search the claimed invention, but which, nevertheless must be in compliance with these rules. Each of these sequences is required to be in the "Sequence Listing". A new "Sequence Listing" and computer-readable-form (CRF) must be submitted in responce to this Office Action.

3. Claim 3 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 is indefinite because it is not clear what DNA of ATCC #75010 the claim is refering to. If the DNA encoding BMP-8 is referred to then the term "characterized by" is vague with regard to whether the protein is one subunit or two and whether the protein has all of the sequence encoding BMP-8 is the deposited strain or only some portion thereof.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for the claimed invention. It is apparent that ATCC accession #75010 is required to practice the claimed invention because claim 3 is limited to its use. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of ATCC accession #75010. See 37 C.F.R. 1.802.

The specification does not provide a repeatable method for obtaining ATCC accession #75010 and it does not appear to be readily available material. Deposit of ATCC accession #75010 would satisfy the enablement requirements of 35 U.S.C. § 112. If a deposit is made under the terms of the Budapest Treaty (see the deposit set forth on p. 34 of the instant specification), then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 C.F.R. 1.808.

If the deposits have not been made under the provisions of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposits will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposits will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CFR 1.809(d), including the full street address of the dopository, should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

6. Claim 3 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

7. Claims 1-5, 10-12 and 26-30 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to wherein a disulfide linked dimer is formed wherein each of the two subunits comprises at least positions 4-142 of SEQ ID NO: 14. See M.P.E.P. §§ 706.03(n) and 706.03(z). The scope of the instant claims is not commensurate with the enablement of the instant specification and the claims broadly encompass a significant number of inoperative species. There is nothing in the instant specification to indicate that peptide portion encoded by the species a) through d) of claim 1 is the portion critical for bone or cartilage forming activity nor that a peptide consisting of the sequence of claim 1 would likely have the disclosed and claimed activity. Thus, it is unpredictable what portion less than the intact natural protein characterized by the aforementioned molecular weight, if any, would have the critical disclosed and claimed activity/utility and it would require undue experimentation to determine which portions of the intact protein, if any, could be excluded and still have activity. The instant claims 1, 2 and 26-29 are not limited with respect to what other amino acids can be present and it is entirely unpredictable if other than the sequence of the natural protein would have activity with these sub-sequences and the essentially infinite scope of the claims therefore encompasses a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence, while retaining similar activity/utility, requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However,

the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and such modifications are unpredictable based on the instant disclosure.
One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. The specification does not support the broad scope of the claims which encompass all derivatives and fragments because the specification does **not** teach (A) the general tolerance to modification and extent of such tolerance; (B) Specific positions and regions of the sequence(s) which can be predictably modified; (C) what fragments, if any, can be made which retain the biological activity of the intact protein; and (D) the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

The remaining claims 3-5, 10-12 and 30 only require that one of the subunits of BMP-8 is a discloses species and is open to wherein any other protein can be the other protein in the dimer. It is not even clear that "BMP-8" limits the protein to being a disulfide-bonded dimer and single chain molecules would be inactive.. However, since a disulfide bonded dimer is

necessary for activity the specification does not support the broad scope of wherein the subunit can be any other protein which provides BMP-8 activity. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027; Ex parte Maizel, 27 USPQ2d 1662 (BPAI, 1993); and Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986). Additionally, while BMP-8 induces cartilage growth, other BMP proteins in the art do not and provide no guidance with regard to how the protein can be modified and the activity retained.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. Claims 1-5, 10-12 and 30 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Oppermann et al. (U.S. Patent No. 5,266,683, hereafter '683). The '683 patent, having priority dates back to 4-8-88 discloses and claims the claimed protein (see the claims, for example, especially claim 24 and SEQ ID NOS: 28 and 29 which refer to hOP2 beginning with Ala which anticipates the instant claims directed to positions 4-142 of SEQ ID NO: 14). This sequence also includes each of the species a) through e) of claim 1, and SEQ ID NO: 28 includes the corresponding

DNA sequences of instant claim 10 and anticipates the products produced thereby. Regarding instant claim 5, see claim 26, which protein comprises or includes -139-142 of instant SEQ ID NO: 14. See also claims 38-40 and 45-49 of the '683 patent.

10. Claims 26-29 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Oppermann et al. (U.S. Patent No.5,354,557, hereafter '557). Similarly to the '683 patent the '557 priority goes back to 4-8-88 and discloses and claim pharmaceutical compositions of the claimed proteins as set forth in the instant claims (see the whole patent, especially claims 48-55). With regard to claim 29, while the '557 patent does not specifically refer to a wound healing effective amount such would have been inherent since the use of the protein was for healing and rejoining bones and/or cartilage which is considered a wound or part of a wound.

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned

by the same person or subject to an obligation of assignment to the same person.

12. Claims 1, 2 and 26-29 are rejected under 35 U.S.C. § 103 as being unpatentable over Oppermann et al. (U.S. Patent 5,011,691) in view of Zoller et al. The reference of Oppermann et al. discloses the recombinant production of various bone morphogenic (i.e. osteogenic) proteins and discloses amino acid sequence alignment of various homologous osteogenic proteins showing what regions are conserved (i.e. likely to be intolerant to substitutions with amino acids of different properties) and non-conserved (i.e. likely to tolerate amino acids substitutions). Oppermann et al. disclose a purified protein designated OP1 in Figure 18-1 having the same sequence in Figure 18-3 as "c)" in claim 1 except that a Gln (Q) residue is present instead of the Lys (K) residue after ACCAPT. However, the comparison of the sequences in Figure 18-3 of Oppermann et al. disclose to one of ordinary skill in the art that variability in the amino acid in the Lys position was tolerated and that lysine (Lys or K) would be an acceptable substitute since this amino acid was present in a number of other homologous sequences of proteins having similar structure/function and therefore a consensus choice amino acid as identified in Figure 18-3, right column. The reference of Zoller et al. discloses conventional site-directed mutagenesis techniques used to substitute one amino acid for another in protein (see whole publication).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute Lys for Gln in the sequence OP1 sequence of Oppermann et al. using the techniques of Zoller et al. or other conventional mutagenesis techniques to obtain a mutein having the osteogenic activity of OP1 because one of ordinary skill in the art would

have been motivated by the expectation of success in obtaining similar structure/function and, therefore, similar results.

Oppermann et al. additionally disclose the use of proteins having these activities in pharmaceutical compositions and the use of a collagenous matrix for supporting such a compositions and providing a surface for bone and/or cartilage formation (see col. 34). Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use such mutein in these compositions.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

14. Papers relating to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-4227. Papers may be submitted Monday-Friday between 8:00 am and 4:45 pm (EST). Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Keith Furman whose telephone number is (703) 308-3453. The examiner can normally be reached on

Monday-Thursday from 7:30 AM-5:00 PM. The examiner can also be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bob Wax, can be reached at (703) 308-4216.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

July 21, 1995

KEITH C. FURMAN, Ph.D.
PRIMARY EXAMINER
GROUP 1800